09/715,764

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Terms	Documents
thymidylate same fluorouracil same express$	9

Database: US Patents Full-Text Database; US Pre-Grant Publication Full-Text Database; JPO Abstracts Database; EPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Refine Search: thymidylate same fluorouracil same express$ Clear

Search History

Today's Date: 7/1/2001

DB Name	Query	Hit Count	Set Name
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	thymidylate same fluorouracil same express$	9	L3
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	thymidylate same fluorouracil same polymorphi$	0	L2
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	thymidylate same fluorouracil	61	L1

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L3: Entry 1 of 9 File: USPT Jun 19, 2001

DOCUMENT-IDENTIFIER: US 6248535 B1
TITLE: Method for isolation of RNA from formalin-fixed paraffin-embedded tissue specimens

BSPR:
Thymidylate synthase is also known to have clinical importance in the development of tumor resistance, as demonstrated by studies that have shown acute induction of TS protein and an increase in TS enzyme levels in neoplastic cells after exposure to 5-FU (Spears et al. 1982; Swain et al. 1989). The ability of a tumor to acutely overexpress TS in response to cytotoxic agents such as 5-FU may play a role in the development of fluorouracil resistance. Previous studies have shown that the levels of TS protein directly correlate with the effectiveness of 5-FU therapy, that there is a direct correlation between protein and RNA expression (Jackman et al, 1985) and that TS expression is a powerful prognostic marker in colorectal and breast cancer (Jackman et al., 1985; Horikoshi et al, 1992).

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L3: Entry 2 of 9 File: USPT Jun 12, 2001

DOCUMENT-IDENTIFIER: US 6245750 B1
TITLE: Enzyme catalyzed therapeutic agents

DEPR:
Methotrexate is a potent inhibitor of dihydrofolate reductase, an enzyme necessary for intracellular folate metabolism. Dihydrofolate reductase functions to regenerate tetrahydrofolate from dihydrofolate, a product of the thymidylate synthase reaction (Voet, et al. eds. (1995), p. 813). It is well established that an important mechanism of resistance of cells to methotrexate is an increase in DHFR activity due to amplification of the DHFR gene. Banerjee, D. et al. (1995), Schimke, R. T. et al. (1988). Lonn, U. et al. (1996) reported that amplification of the DHFR gene occurred in breast cancer patients who previously received adjuvant chemotherapy (cyclophosphamide, methotrexate, 5-fluorouracil [CMF]) after surgery. Lack of the retinoblastoma (Rb) may also lead to enhanced MTX resistance as a consequence of an increase in DHFR mRNA expression activity without gene amplification. Li, W. W. et al. (1995). Cell lines with mutated p53 have been shown to undergo gene amplification, and the resistant cells are selected by chemotherapy. Banerjee, D. et al. (1995), Yin, Y. et al. (1992) and Livingston, L. R. et al. (1992). For the purposes of performing the assay of this invention, Schimke, R. T. et al. (1988) describes several mouse, hamster and human cell lines. Alternatively, the PCR method of Lonn U. et al. (1996) is used to assay DHFR gene amplification and identify cells that are useful in the method of identifying therapeutic agents as described herein. The nucleotide sequence of the cDNA coding for the human dihydrofolate reductase is provided in Masters, J. N. and Attardi, G. (1983) and cells can be engineered to express varying levels of the enzyme as noted herein. Dicken, A. P. et al. (1993) describes a mutant DHFR gene selected by chemotherapy. Purification of DHFR and assays related to enzyme function are described in Nakano, T. et al. (1994). Alternatively, cDNA encoding DHFR is transfected into NIH 3T3 cells. Candidate drugs are added in varying concentrations and cell killing and inhibition of proliferation are assayed.

DEPR:
The overexpression of thymidylate synthase is associated with colon cancer, breast cancer, gastric cancer, head and neck cancer, liver cancer and pancreatic cancer. These diseases are currently treated by antimetabolite drugs (uracil-based, folate-based, or quinazoline-based, (see Table 1)). In each of these cases it is likely that tumor suppressor loss and/or 5-fluorouracil therapy can lead to amplified activity of TS, or select for drug resistant forms of the enzyme, and thereby lead to drug-resistance of the disease relapse. Lonn, U. et al. (1996) reported that amplification of the TS gene occurred in breast cancer patients who previously received adjuvant chemotherapy (cyclophosphamide, methotrexate, 5-fluorouracil [CMF]) after surgery. This enhanced TS expression is in addition to the basic increase of TS which results from loss of tumor suppressor function. The principal reaction normally performed by TS is the synthesis of deoxythymidine monophosphate (dTMP) and dihydrofolate (DHF) from deoxyuridine monophosphate (dUMP) and N(5),N(10)-methylene-tetrahydrofolate (THF). In one embodiment, a derivative of uracil or THF is provided to cells expressing TS. For purposes of this invention, "uracil" (base only) and "uridine" (base and sugar) are used interchangeably and synonomously. Table 4 (below) summarized the many cancer types impacted by elevated TS expression.

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L3: Entry 4 of 9 5,998,151 File: USPT Dec 7, 1999

DOCUMENT-IDENTIFIER: US 5998151 A
TITLE: Methods for predicting the efficacy of a chemotherapeutic regimen for gastrointestinal cancers using antibodies specific for thymidylate synthase

DEPR:
This example illustrates the correlation between thymidylate synthase expression levels and a patient's response to a therapeutic regimen containing 5-fluorouracil.

DETL:
TABLE 4 _____ Thymidylate Synthase Expression Correlation With 5-Fluorouracil Response 5-Fluorouracil TS TS Parameter Exposure Response.sup.a N Expression.sup.b P.sub.2.sup.c _____ Total (TS.sub.T) Pre None 5 5.5 .+-. 1.6 0.031 MR, PR 8 0.7 .+-. 0.34 Total (TS.sub.T) Post None 5 10.2 .+-. 3.5 0.16 MR, PR 8 3.1 .+-. 0.4 Free (TS.sub.F) Post None 5 3.4 .+-. 1.7 0.019 MR, PR 8 0.3 .+-. 0.1 Complexed Post None 5 6.8 .+-. 1.9 0.164 (TS.sub.B) MR, PR 8 2.8 .+-. 0.34 Bound Fraction Post None 5 75.6 .+-. 7.4 0.056 (TS.sub.B /TS.sub.T) MR, PR 8 91.9 .+-. 1.7 _____ .sup.a MR, minor response; PR, partial response .sup.b Thymidylate synthase (TS) values are expressed as mean SEM .sup.c P.sub.2 values measured by Wilcoxon rank sum test

ORPL:
Johnston, Patrick G., et al. (1995) "Thymidylate Synthase Gene and Protein Expression Correlate and Are Associated with Response to 5-Fluorouracil in Human Colorectal and Gastric Tumors", Cancer Research 55:1407-1412.

ORPL:
Johnston, P.G., et al. (1994) "Thymidylate Syntase Protein and Gene Expression Predicts for Response to 5-Fluorouracil Leucovorin Chemotherapy in Patients with Colorectal and Gastric Cancer", Proceedings of ASCO 13:196 (569).

L3: Entry 4 of 9 File: USPT Dec 7, 1999

US-PAT-NO: 5998151
DOCUMENT-IDENTIFIER: US 5998151 A

TITLE: Methods for predicting the efficacy of a chemotherapeutic regimen for gastrointestinal cancers using antibodies specific for thymidylate synthase

DATE-ISSUED: December 7, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Johnston; Patrick G.	Bethesda	MD	N/A	N/A
Allegra; Carmen J.	North Potomac	MD	N/A	N/A
Fisher; Edwin R.	Pittsburgh	PA	N/A	N/A

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
The United States of America as represented by the Department of Health and Human Services	Washington	DC			06

APPL-NO: 8/ 758034
DATE FILED: November 27, 1996

PARENT-CASE:
This application claims the benefit of U.S. Provisional Application No. 60/007,285, filed Dec. 1, 1995, the disclosure of which is incorporated by reference.

INT-CL: [6] G01N 33/53, C07K 1/00, C07K 16/00
US-CL-ISSUED: 435/7.1; 435/7.23, 435/7.5, 435/7.92, 530/387.1, 530/391.1, 530/350
US-CL-CURRENT: 435/7.1; 435/7.23, 435/7.5, 435/7.92, 530/350, 530/387.1, 530/391.1

FIELD-OF-SEARCH: 530/387.1, 530/391.1, 530/350, 435/7.1, 435/7.23, 435/7.5, 435/7.92

PRIOR-ART-DISCLOSED:

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Johnston, Patrick G., et al. (1992) "Immunological Quantitation of Thymidylate Synthase Using the Monoclonal Antibody TS 106 in 5-Fluorouracil-sensitive and--resistant Human Cancer Cell Lines", Cancer Research 52:4306-4312.
Johnston, Patrick G., et al. (1994) "The Role of Thymidylate Synthase Expression in Prognosis and Outcome of Adjuvant Chemotherapy in Patients with Rectal Cancer", Journal of Clinical Oncology, 12(12):2640-2647.
Johnston, Patrick G., et al. (1995) "Thymidylate Synthase Gene and Protein Expression Correlate and Are Associated with Response to 5-Fluorouracil in Human Colorectal and Gastric Tumors", Cancer Research 55:1407-1412.
Kelsen, David, et al. (1992) "FAMTX Versus Etoposide, Doxorubicin, and Cisplatin: A Random Assignment Trial in Gastric Cancer", Journal of Clinical Oncology 10(4):541-548.
Silberman, L. Leichman, et al. (1992) "Preoperative Systemic Chemotherapy Followed by Adjuvant Postoperative Intraperitoneal Therapy for Gastric Cancer: A University of Southern California Pilot Program", Journal of Oncology 10(2):1933-1942.
Lerner, Adam, et al. "Etoposide, Doxorubicin, and Cisplatin Chemotherapy for Advanced Gastric Adenocarcinoma: Results of a Phase II Trial", Journal of Oncology, 10(4):536-540.
Romain, Sylvie, et al. (1997) "DNA-Synthesis Enzyme Activity: A Biological Tool Useful for Predicting Anti-Metabolic Drug Sensitivity in Breast Cancer?", Int. J. Cancer (Pred. Oncol)74:156-161.
Swain, S.M., et al. (1989) "Flurouracil and High-Dose Leucovorin in Previously Treated Patients with Metastatic Breast Cancer", Journal of Clinical Oncology 7(7):890-899.
Wilke, H., et al. (1989) "Preoperative Chemotherapy in Locally Advanced and Nonresectable Gastric Cancer: A Phase II Study with Etoposide, Doxorubicin, and Cisplatin", Journal of Clinical Oncology, 7(():1318-1326.
Keyomarsi, K., et al. (1991) "Differential Expression of Thymidylate Synthase Message Versus Protein in Synchronized Human Breast Cancer Cells", J. Cell Biol. 115 (3 Part 2): 206A.
Kang, Y.K. et al. (1992) "The Effect of Neoadjuvant Chemotherapy on the Surgical Outcome of Locally Advanced Gastric Adenocarcinoma: Interim Report of a Randomized Controlled Trial", Proceedings of ASCO 11:173 (505).
Johnston, P.G., et al. (1994) "Thymidylate Syntase Protein and Gene Expression Predicts for Response to 5-Fluorouracil Leucovorin Chemotherapy in Patients with Colorectal and Gastric Cancer", Proceedings of ASCO 13:196 (569).
Ajani, J.A., et al. (1992) "Preoperative and Postoperative Chemotherapy (CT) for Patients with Potentially Resectable Gastric Carcinoma", Proceedings of ASCO 11:165 (475).

ART-UNIT: 162
PRIMARY-EXAMINER: Hutzell; Paula K.
ASSISTANT-EXAMINER: Ungar; Susan
ATTY-AGENT-FIRM: Townsend and Townsend and Crew, LLP

ABSTRACT:

Methods for determining whether a chemotherapeutic treatment is appropriate for patients afflicted with gastrointestinal cancers, comprising;

(a) obtaining a solid tumor tissue sample from the patient;

(b) measuring a thymidylate synthase expression level in the tissue sample; and

(c) comparing the thymidylate synthase expression level with a group of standard tumor tissue samples, the standards having known thymidylate synthase expression levels and known responses to the chemotherapeutic treatment, to determine if that chemotherapeutic treatment is appropriate for the patient.

11 Claims, 5 Drawing figures

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L3: Entry 6 of 9 File: USPT Oct 5, 1999

DOCUMENT-IDENTIFIER: US 5962246 A
TITLE: dUTPase, its isoforms, and diagnostic and other uses

ORPL:
Johnston, et al., Thymidylate Synthase Gene and Protein Expression Correlate and Are Associated with Response to 5-Fluorouracil in Human Colorectal and Gastric Tumors, Cancer Research 55: 1407-1412, 1995.

L3: Entry 8 of 9 File: USPT Aug 24, 1999

DOCUMENT-IDENTIFIER: US 5942389 A
TITLE: Genes and genetic elements associated with sensitivity to cisplatin

DEPV:
GSE HL7.11 (SEQ ID NO:16) is an antisense-oriented fragment (see FIG. 23) of a previously-isolated cDNA encoding dihydroorotate dehydrogenase (DHOD, SEQ ID NO:20; Minet et al., 1992, Gene 121: 393-396). This enzyme catalyzes an intermediate step in the biosynthesis of uridylic acid (UMP) and deoxyuridylic acid (dUMP). It is known that the conversion of dUMP to TMP, catalyzed by thymidylate synthetase (TS) in conjunction with dihydrofolate reductase (DHFR) is a critical step in DNA synthesis, and provides a biochemical target for several anticancer drugs, including 5-fluorouracil and methotrexate. Changes in the intracellular folate pool have been associated with exposure to cisplatin, and some cisplatin-resistant cells have been reported to express increased amounts of both TS and DHFR (see Scanlon et al., 1986, Proc. Natl. Acad. Sci. USA 83: 8923-8927). Inhibition of DHOD by the antisense GSE disclosed herein would be expected to decrease the intracellular concentration of UMP and dUMP and thus affect the activity of TS and DHFR and the intracellular folate pool. These results support the hypothesis that folate pool perturbations and TS activity play a role in the cellular response to cisplatin, but provide a heretofore unexpected target for cisplatin sensitivity in tumor cells.

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Search Results -

Terms	Documents
thymidilate same polymorphism	0

Database: US Patents Full-Text Database; US Pre-Grant Publication Full-Text Database; JPO Abstracts Database; EPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Refine Search: thymidilate same polymorphism Clear

Search History

Today's Date: 7/1/2001

DB Name	Query	Hit Count	Set Name
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	thymidilate same polymorphism	0	L4
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	thymidilate same vntr	0	L3
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	thymidilate same tandem adj2 repeat	0	L2
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	thymidilate same fluorouracil	4	L1

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L9: Entry 12 of 37 File: USPT Dec 1, 1998

DOCUMENT-IDENTIFIER: US 5843654 A
TITLE: Rapid detection of mutations in the p53 gene

DEPR:
The description of the invention is divided into: I. Detection of Specific Nucleic Acid Sequences Using 5' Nucleases; II. Generation of 5' Nucleases Derived From Thermostable DNA Polymerases; III. Therapeutic Uses of 5' Nucleases; IV. Detection of Antigenic or Nucleic Acid Targets by a Dual Capture Assay; and V. Cleavase.TM. Fragment Length Polymorphism for the Detection of Secondary Structure and VI. Detection of Mutations in the p53 Tumor Suppressor Gene Using the CFLP.TM. Method. To facilitate understanding of the invention, a number of terms are defined below.

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L9: Entry 19 of 37 File: USPT Feb 13, 1996

DOCUMENT-IDENTIFIER: US 5491064 A
TITLE: HTS-1 gene, a human tumor suppressor gene

ABPL:
A gene which is associated with tumor suppression and is localized on chromosome 11 has now been identified. The identification, localization and sequence of a gene which demonstrates differential expression in a manner that correlates with tumorigenicity suggests that this gene could potentially be used for gene therapy in cancers deleted or altered in their expression of the gene. Furthermore, a gene which is localized on chromosome 11p15, with identified polymorphisms, could be used for analysis of tumor DNA for loss of heterozygosity at chromosome 11p15. This region of chromosome 11 shows frequent loss of heterozygosity (LOH) in many human malignancies. Thus, the determination of LOH at chromosome 11p15 may be useful in predicting the prognosis of that tumor.

BSPR:
A gene which is associated with tumor suppression and is localized on chromosome 11 has now been identified. The identification, localization and sequence of a gene which demonstrates differential expression in a manner that correlates with tumorigenicity suggests that this gene could potentially be used for gene therapy in cancers deleted or altered in their expression of the gene. Furthermore, a gene which is localized on chromosome 11p15, with identified polymorphisms, could be used for analysis of tumor DNA for loss of heterozygosity at chromosome 11p15. This region of chromosome 11 shows frequent loss of heterozygosity (LOH) in many human malignancies. See, Junien, et al., Genomics, 12:620-625 (1992). Thus, the determination of LOH at chromosome 11p15 may be useful in predicting the prognosis of that tumor.

L9: Entry 21 of 37 File: USPT Dec 21, 1993

DOCUMENT-IDENTIFIER: US 5272057 A
TITLE: Method of detecting a predisposition to cancer by the use of restriction fragment length polymorphism of the gene for human poly (ADP-ribose) polymerase

DEPR:
In one embodiment of this invention, the progression of a tumor's pathogeneity in tumor biopsy samples can be followed. By examining the changes in the polymorphic bands in patients with cancer, this method can be used for monitoring tumor therapy in diseases such as metastatic cancer, solid tumors, and AID's related lymphomas. Thus, the probe can be used in the method of this invention to establish the polymorphisms in the tumor sample. After treatment for cancer, by chemotherapy or radiotherapy, the biopsy tumor sample can again be assayed for the presence of the polymorphisms. Using the HindIII restriction enzyme, for example, it has been determined that in cancer patients who have an ab pattern before treatment (with bands showing at 2.6 and 2.9 kb), there is a loss of the 2.9 kb (a) band after treatment, with a concomitant reduction in the pathogenicity of the tumor.

WEST

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L9: Entry 22 of 37 File: EPAB Feb 13, 1996

DOCUMENT-IDENTIFIER: US 5491064 A
TITLE: HTS-1 gene, a human tumor suppressor gene

FPAR:
A gene which is associated with tumor suppression and is localized on chromosome 11 has now been identified. The identification, localization and sequence of a gene which demonstrates differential expression in a manner that correlates with tumorigenicity suggests that this gene could potentially be used for gene therapy in cancers deleted or altered in their expression of the gene. Furthermore, a gene which is localized on chromosome 11p15, with identified polymorphisms, could be used for analysis of tumor DNA for loss of heterozygosity at chromosome 11p15. This region of chromosome 11 shows frequent loss of heterozygosity (LOH) in many human malignancies. Thus, the determination of LOH at chromosome 11p15 may be useful in predicting the prognosis of that tumor.

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Search Results -

Terms	Documents
l8 not l6	37

Database: US Patents Full-Text Database; US Pre-Grant Publication Full-Text Database; JPO Abstracts Database; EPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Refine Search: l8 not l6 Clear

Search History

Today's Date: 7/1/2001

DB Name	Query	Hit Count	Set Name
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	l8 not l6	37	L9
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	tumor same polymorphism same therap$	39	L8
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	tumor same polymorphism same chemotherap$	4	L7
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	tumor same polymorphism same drug	5	L6
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	tumor same polymorphism	326	L5
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	thymidilate same polymorphism	0	L4
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	thymidilate same vntr	0	L3
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	thymidilate same tandem adj2 repeat	0	L2
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	thymidilate same fluorouracil	4	L1

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L1: Entry 1 of 4 File: USPT Mar 20, 2001

DOCUMENT-IDENTIFIER: US 6203991 B1
TITLE: Inhibition of smooth muscle cell migration by heme oxygenase I

DRPR:
Herpes simplex virus thymidine kinase (HSV-tk) converts an inert nucleoside analog, ganciclovir into a phosphorylated, toxic form in transduced cells. Its subsequent incorporation into the host DNA induces chain termination and cell death in dividing cells, while non-dividing cells remain unaffected. Local delivery of recombinant adenovirus encoding for HSV-tk at the time of the balloon injury and systemic administration to ganciclovir inhibited smooth muscle cell proliferation in vivo, and decreased intimal formation in balloon-injured porcine and rat arteries and atherosclerotic rabbit arteries. A similar reduction of neointimal hyperplasia was observed in arterial interposition grafts which overexpress HSV-tk in the rabbit. Cytosine deaminase (CD) catalyzes the hydrolytic deamination of non-toxic cytosine and 5-fluorocytosine (5-FC) into uracil and 5-fluorouracil, which inhibits thymidilate synthase and hence DNA and RNA synthesis. In human and rabbit primary smooth muscle cells, CD/5-FC does not induce significant necrosis or apoptosis but results in cytostatic effects on vascular smooth muscle cells. CD gene transfer in the rabbit femoral injury model followed by systemic 5-FC treatment resulted in a decrease of the intima to media area ratio, comparable to the efficacy of HSV-tk/ganciclovir in a rat and pig model of vascular injury.